Cost-Effectiveness of Olorofim in Invasive Aspergillosis Patients Lacking Suitable Alternative Treatment Options from a US Payer Perspective

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Background

Invasive aspergillosis (IA), despite the recent improvements in treatment and diagnostics, remains a devastating disease and is the most common invasive fungal infection (IFI) caused by molds. Nearly 9,000 hospitalizations for IA are reported in the US each year, with treatment costs exceeding $80,000 per stay and an inpatient mortality rate surpassing 12%.[1, 2]

The emergence of rising IA cases is paralleled by the increasing number of immunocompromised patients (i.e., vulnerable hosts) and frequency of triazole resistance. Treatment options for IA currently consist of three classes of antifungal agents: azoles, polyenes, and echinocandins. Novel therapies are urgently needed especially in settings of difficult-to-treat IA, comprising refractory or resistant disease, drug-drug interactions, and hepatic and renal toxicities. Promising new drugs are in late-stage clinical development, including olorofim, an oral antifungal studied in IA patients with no available treatment options.[1]

Olorofim acts as a potent selective inhibitor of the type 2 fungal dihydro-orotate dehydrogenase enzyme. The open-label, single-arm, Phase IIb study (NCT03583164, Study 32) evaluated the efficacy and safety of olorofim for the treatment of IFI lacking suitable alternative treatment options, including patients with either proven IA or probable lower respiratory tract IA.[3]

Objective

To measure the **cost-effectiveness** of olorofim compared to best available antifungal therapy (BAAT) from a US payer perspective.

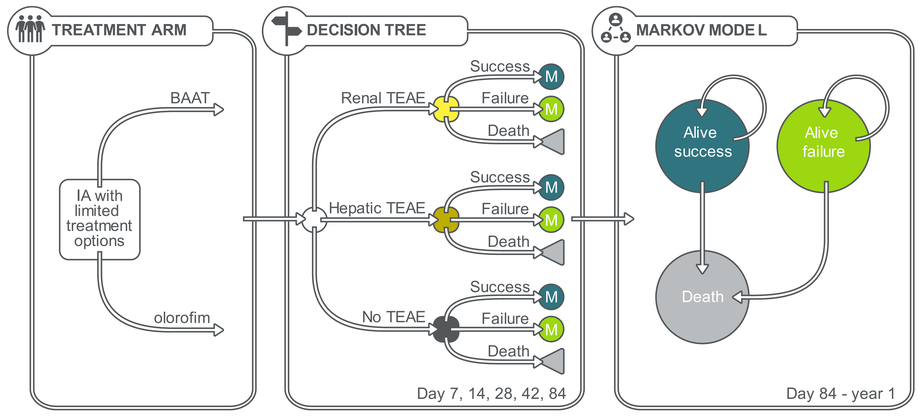
Method

The analysis focused on IA patients lacking suitable alternative options due to refractory IA, resistant IA, or inability to use available antifungals due to intolerance or drug-drug interactions.[3] The model was developed in Microsoft Excel software and relied on a hybrid decision tree-Markov structure. The decision tree (i.e., treatment phase) time points corresponded to the Study 32 assessment visits (days 7, 14, 28, 42 and 84) and was followed by a three-state Markov model (i.e., follow-up phase), where patients moved between the 'success', 'failure' and 'death' health states until the end of the one-year time horizon. The comparator arm (BAAT) consisted of antifungal therapies including: liposomal formulation of amphotericin B, echinocandin, and anti-mold triazole, alone or in combination.[4]

1. **Treatment phase**: within each treatment arm, patients were distributed based on the treatment-specific probability of experiencing hepatic treatment-emergent adverse events (TEAEs), renal TEAEs or no TEAEs and then, at each time point, moved between the defined health states (treatment success, treatment failure or death). The flow of the patients through the decision tree dictated the accrual of costs associated with treatment, hospitalization (general ward and ICU), TEAE and IV drug administration at home. The lowest average wholesale prices (AWPs) were assigned to BAAT's treatment costs and AmBisome™ was used as a proxy for olorofim pricing.
2. **Follow-up**: patients were assumed to stay in the same success /failure state they achieved at the end of the decision tree or to die (no relapse). The applied monthly mortality rate (-0.016) was treatment independent. No costs were accrued in this phase.

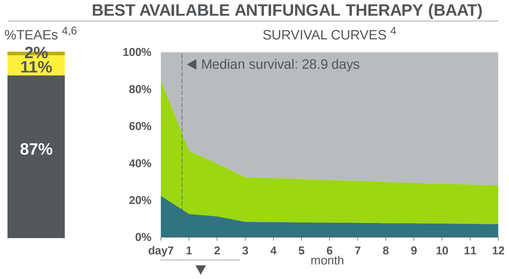
Accrual of hospital stays across health states was estimated using Poisson regressions fitted on Study 32 data.[3] Mortality on treatment was estimated using parametric survival models fitted on Study 32 data and Walsh et al. for olorofim and BAAT respectively.[3, 4] Utility values were derived from EQ-5D scores from Study 32 and assigned to each health state.[3] A utility decrement (-0.023) was applied to the patients on IV therapies.[5]

Model structure



Inputs

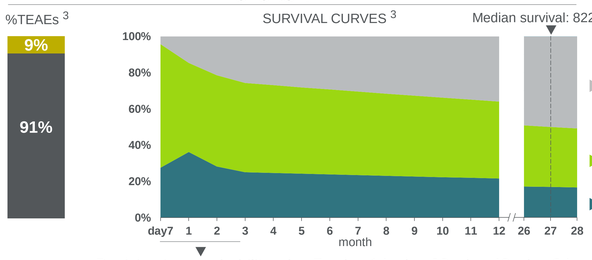
BEST AVAILABLE ANTIFUNGAL THERAPY (BAAT)



Decision tree probability

	day 7	day 14	day 28	day 42	day 84
of success	22.4%	19.8%	12.5%	11.3%	8.3%
of failure	65.2%	57.4%	36.5%	33.0%	24.2%
of death	12.4%	22.8%	51.0%	55.7%	67.5%

OLOROFIM



Decision tree probability

	day 7	day 14	day 28	day 42	day 84
of success	27.6%	37.6%	36.2%	28.2%	25.0%
of failure	68.4%	57.4%	52.9%	53.0%	49.3%
of death	4.0%	5.0%	10.9%	18.8%	25.7%

Hepatic TEAE Renal TEAE No TEAE Success Failure Death

COSTS

Treatment		
BAAT	$2,261.95	[4, 7]
olorofim	$907.00	*
IV at home	$64.72 /day	[8]
Hospitalization **		
Ward	$3,204 /day	[9]
ICU	$6,408 /day	[10]
TEAEs **		
Hepatic	$135	[8]
Renal	+7 ward days	[11]

* Assumed same price as AmBisome™

** Non-treatment-specific inputs

LOS** †

	Ward [3]	ICU [3]	UTILITY [3] **
Death	27.0	3.7	0
Failure	29.1	3.2	0.59
Success	16.4	1.6	0.63

† days accrued at the end of the decision tree (84 days)

Results

The estimated 1-year **cost** of treating proven or probable IA in patients lacking suitable alternative options was $167,971 (olorofim) and $208,696 (BAAT), for an incremental cost of -$40,725. **QALYs** were 0.46 and 0.22, respectively, making olorofim the dominant (less costly, more effective) strategy.

The most significant difference in costs was in the **drug acquisition**, with olorofim being $44,770 less costly than the comparator. The olorofim arm resulted in slightly higher **healthcare resource** costs, with an increment of $4,578 (+4.7%). This result was expected since olorofim improved survival, resulting in more costs related to in-hospital stays.

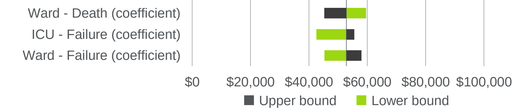
	Total costs	LYs	QALYs	ICER	INMB
BAAT	$208,696	0.370	0.220	olorofim dominates	$52,827
olorofim	$167,971	0.764	0.462		
Incremental	-$40,725	0.393	0.242		

Sensitivity and scenario analyses

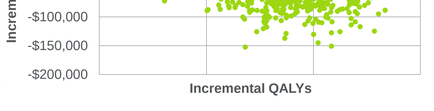
The direction of the results (i.e., olorofim cost-effective vs BAAT) was maintained in all **DSA** scenarios and in the vast majority of the **PSA** simulations (97.5% of 1,000 iterations) given the willingness to pay (WTP) threshold of $50,000 per QALY.

Three **scenario analyses** were undertaken: 1) extending the time horizon to 5 years; 2) using a hospital perspective (28 days time horizon) instead of the payer perspective; 3) applying a hospital perspective and using alternative historic control data for the BAAT arm. In all scenarios, olorofim was found to be dominant with an INMB of $80,082, $41,763, and $38,705 respectively.

DETERMINISTIC SENSITIVITY ANALYSIS (DSA)



PROBABILISTIC SENSITIVITY ANALYSIS (PSA)



Conclusion

When available and price parity with AmBisome™ is assumed, olorofim is a cost-effective alternative to best available antifungal therapy for IA with limited treatment options from a US payer perspective. Olorofim resulted in lower drug therapy costs, equivalent cost related to ICU stays and improved quality of life when compared to best available antifungal therapy.

Assumptions and limitations

- No population adjustment was carried out between Study 32 and the studies used for the BAAT outcomes (Walsh et al.).
- The model did not consider: treatment switch/discontinuation, dosing adjustment, retreatment, drug waste and probability of relapse.
- Same efficacy and safety were assigned to all treatments included in the BAAT arm.
- Ward/ICU LOS and mortality rate (Markov model) were treatment-independent.
- TEAEs did not affect the health state occupancy and utility.
- Patients receiving olorofim were not at risk of renal TEAE (i.e., not at risk of renal toxicity).
- Occurrence of renal TEAEs accrued additional general ward days, but not ICU days, while hepatic TEAEs were associated with a cost increase only.

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Acronyms and abbreviations

AWP	Average wholesale price
BAAT	Best available antifungal therapy
DSA	Deterministic sensitivity analysis
IA	Invasive aspergillosis
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IFI	Invasive fungal infections
INMB	Incremental net monetary benefit
IV	Intravenous
LOS	Length of stay
LY	Life years
PSA	Probabilistic sensitivity analyses
QALY	Quality-adjusted life years
TEAE	Treatment emergent adverse event
WTP	Willingness to pay

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